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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,417	03/30/2004	Po-Ying Chan-Hui	131.03US	5640

33603 7590 07/12/2006

MONOGRAM BIOSCIENCES
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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/813,417	CHAN-HUI ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *8-13,16-29,35,36,39,44 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,14,15,30-34,37,38 and 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 6/23/04; 8/30/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed April 26, 2006 in response to the Office Action of March 1, 2006 is acknowledged and has been entered. Applicants elected Group I without traverse and the patient sample species of fixed tissue sample, the ErbB receptor complex species of Her2-Her2 homodimers, and the cancer species of breast cancer.

Claims 1-45 are pending. Claims 8-13, 16-29, 35, 36, 39, 44, and 45 are withdrawn from further consideration by the examiner under 35 CFR 1.142(b) as being drawn to non-elected inventions and species. Claims 1-7, 14, 15, 30-34, 37, 38, and 40-43 are currently under prosecution.

Specification

2. The disclosure is objected to because of the following informalities: **Figures 5B and 5C** are missing the labels for "Normal" and "Tumor" above the middle column of graphs for Her1-Her2 Dimers. Appropriate correction is required.

3. The disclosure is objected to because of the following informalities: **Figures 10A-10C** are missing a legend or explanation in the "Brief Description of the Drawings" of the symbols or data points in the graphs. It is unclear what heterodimer each point represents. There is no explanation of these figures in Example 6 on page 54 which refers to these figures. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-7, 14, 15, 30-34, 37, 38, and 40-43 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a correlation step describing how the results of the assay relate back to the preamble of the method objectives. It is unclear what the relative amount of ErbB cell surface receptor of the patient sample is to the reference sample and what status of disease it determines because there is no correlation step.

5. Claims 4-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 recites the phrase "having a cleavage-inducing moiety with an **effective proximity**" and it is unclear what its effective proximity is to.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 2, 30-33, 37, 38, 40-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of **diagnosing the presence of breast cancer** comprising measuring directly in a patient sample an amount of **Her1-Her2 or Her2-Her3 complex**, comparing the amount to its corresponding amount in a reference sample, correlating difference in the amount from the patient sample and the respective corresponding amount from the reference sample, **wherein an increase in the amount of Her1-Her2 or Her2-Her3 complex indicates the presence of breast cancer in a patient**, does not reasonably provide enablement for a method of determining the disease status of a patient suffering from a disease characterized by abberant expression of one or more ErbB cell surface receptors complexes comprising measuring directly in a patient sample an amount of each of one or more ErbB cell surface receptor complexes, comparing each such amount to its corresponding amount in a reference sample, correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status of the patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not

'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of determining the disease status of a patient suffering from a disease characterized by abberant expression of one or more ErbB cell surface receptors complexes comprising measuring directly in a patient sample an amount of each of one or more ErbB cell surface receptor complexes, comparing each such amount to its corresponding amount in a reference sample, correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status of the patient. The claims are broadly drawn to a method of determining **any disease status** or **any status** of **any cancer** based on **any increase or any decrease in the amounts** of **any ErbB cell surface receptor complex** relative to a control amount. While dependent claims may further limit method steps or types of cancer, they do not limit all of the variables listed in bold above.

The specification discloses that "disease status" includes but is no limited to the likelihood of contracting a disease, the presence or absence of a disease, prognosis of disease severity, and likelihood that a patient will respond to treatment by a particular therapeutic agent that acts through the receptor complex (p. 8, line 35 through p. 9, line 2). Examples 2 and 10 of the specification disclose the detection of Her1-Her2 and Her2-Her3 heterodimers in tissue lysates from human breast cancer patients, wherein a significant number of the breast cancer specimens had an increase in the amount of Her1-Her2 and Her2-Her3 heterodimers as compared to normal tissue amounts (p. 47, lines 10-19; Figures 5A-5C; p. 59, lines 5-10; Figures 14A and 14B).

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification does not provide examples or guidance for determining the disease status of a patient comprising measuring directly in a patient sample an amount of each of one or more ErbB cell surface receptor complexes and comparing the amount to a reference sample other than for diagnosing the presence of breast cancer comprising detecting increased amounts of Her1-Her2 or Her2-Her3 heterodimers in patient breast cancer samples.

Holbro et al (PNAS, 2003, 100:8933-8938) teach that the Her2-Her3 (ErbB2/ErbB3) dimer functions as an oncogenic unit to drive breast cell proliferation (abstract). Hudelist et al (Breast Cancer Research and Treatment, 2003, 80:353-361) teach that the coexpression of Her2 and Her3 is particularly strong in nodal positive tumors which indicates a key role of the heterodimer in breast tumor progression and demonstrate that Her2 is the preferred co-expression partner in nodal-positive tumors

and the most likely dimerization candidate in malignant breast tumors (abstract, p. 360, col. 1). Alimandi et al (Oncogene, 1995, 10:1813-1821) teach that Her2 and Her 3 cooperate in neoplastic transformation, that cooperation between the two involves heterodimerization, and that Her3 activates Her2 transforming potential at intermediate expression levels and substantially enhances neoplastic transformation (abstract; p. 1819, col. 1). Way et al (Future Oncol, 2005, 1:841-849) teach that expression of Her3 is seen in many of the same tumor types that overexpress Her2 and mammary tumors of transgenic mice expressing transforming Her2 mutants exhibit selective upregulation of Her3 expression and activity, suggesting there might be a selective advantage/pressure leading to coexpression of both receptors (p. 843, col. 2). Way et al teach that the detection of both Her2 and Her3 may have more clinical and prognostic significance than the detection of either protein alone (p. 845, col. 1) and overexpression of Her2 increases the number of Her2-Her3 heterodimers thereby increasing Her2 signaling which leads to neoplastic growth (p. 847, col. 1 to 2). Zhan et al (Cancer research, 2006, 66:5201-8) teach that the coexpression of Her1 (ErbB1) with Her2 (ErbB2) may critically regulate invasive progression of ErbB-positive breast cancers (abstract). Although the art does not teach the detection of the heterodimers in patient breast cancer samples, it is clear that heterodimers Her1-Her2 and Her2-Her3 play a role in breast cancer progression, that each receptor is present in most breast cancer samples, and that the receptors readily dimerize with each other.

Regarding a method of determining "disease status" wherein disease status indicates the "likelihood of contracting a disease", "prognosis of disease severity" or

likelihood that a patient will respond to treatment by a particular therapeutic agent that acts through a receptor complex", as defined by the specification, the specification provides neither guidance on nor exemplification of how to correlate the amount of an ErbB cell surface receptor complex to the likelihood of contracting a disease, prognosis of disease severity, or likelihood that a patient will respond to treatment by a particular therapeutic agent. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714,

see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). In addition, Slamon et al. (Science Vol. 235, January 1987, pages 177-182) teach other essential factors that are known to be important in the prognosis of breast cancer in individual patients such as size of the primary tumor, stage of the disease at diagnosis, hormonal receptor status, and number of axillary lymph nodes involved with disease (page 178, 1st column, 2nd paragraph). Such data are critical to assessing actuarial curves for relapse (Figure 3), and for comparing disease-free survival and overall survival to prognostic factors (Table 4).

Given the disclosure of the specification and teaching in the art, one of skill in the art could not predictably determine any disease status of a patient comprising measuring in a patient sample an amount of any one or more ErbB cell surface receptor complexes upon comparison to a correlating amount in a reference sample.

Therefore, in view of the breadth of the claims, lack of guidance in the specification, the absence of working examples, and the state of the art, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

7. Claims 3-7, 14, 15, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of determining the disease status of a patient suffering from a disease characterized by abberant expression of one or more ErbB cell

surface receptors complexes comprising measuring directly in a patient sample an amount of each of one or more ErbB cell surface receptor complexes, comparing each such amount to its corresponding amount in a reference sample, correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status of the patient, wherein said one ErbB cell receptor complex is a Her2-Her2 homodimer.

The specification discloses the detection of Her2-Her2 homodimers in cell lysates of cell culture (Example 3, p. 47) and in sections from fixed pellets of breast cancer cell lines MCF-7 and SKBR-3, wherein the SKBR3 cells express higher levels of Her2-Her2 homodimers than MCF-7 cells (Example 11; p. 61, lines 8-15; Figure 15B), and wherein it is known that SKBR-3 cells overexpress Her2 and MCF-7 express low levels of Her2 (p. 47, lines 24-27).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide examples or guidance for determining the disease status of a patient comprising measuring directly in a patient sample an amount of **Her2-Her2 homodimer**, comparing the amount of Her2-Her2 homodimer to a reference amount, and correlating the difference in the amount from the patient sample and the respective corresponding amount from the reference sample to the disease status of the patient. The specification only exemplifies assay techniques for measuring amounts of Her2-Her2 homodimers in cell culture that is known to express Her2. The specification does not provide a nexus between the disease status of

a patient and the amount of Her2-Her2 dimer in a patient sample as compared to a control.

Holbro et al (supra) demonstrate that Her2 overexpression and activity alone are insufficient to promote breast tumor cell division (abstract), and Her2 heterodimers, particularly Her2-Her3, function as an oncogenic unit to drive breast tumor cell proliferation. Way et al (supra) teach that the detection of both Her2 and Her3 may have more clinical and prognostic significance than the detection of either protein alone (p. 845, col. 1) and overexpression of Her2 increases the number of Her2-Her3 heterodimers, thereby increasing Her2 signaling which leads to neoplastic growth (p. 847, col. 1 to 2). Despite overexpression of Her2 alone, Holbro et al teach that this condition was not sufficient to promote breast tumor cell division, hence, it is unclear how the amount of Her2-Her2 homodimers would could be used predictably as a biomarker for determining the disease status of a patient. Way et al teach that an increase in the amount of Her2 alone promotes heterodimer formation with other receptors such as Her3 which would increase Her2 signaling and leads to neoplastic growth. Given the teaching of the art and disclosure of the specification one could not predictably determine disease status of a patient comprising measuring directly in a patient sample an amount of Her2-Her2 homodimer, comparing the amount of Her2-Her2 homodimer to a reference amount, and correlating the difference in the amount from the patient sample and the respective corresponding amount from the reference sample to the disease status of the patient.

Therefore, in view lack of guidance in the specification, the absence of working examples, and the state of the art, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Double Patenting

8. Claims 37 is objected to under 37 CFR 1.75 as being a substantial duplicate of claims 33. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-7, 14, 15, 30-34, 37, 38, 40-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. **10/813412.** Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of Application No. **10/813412** are drawn to a method of determining disease status of a patient suffering from a disease characterized by abberant expression of one or more Her receptor heterodimers comprising measuring directly in a patient sample an amount of each of one or more Her receptor heterodimers, comparing each such amount to its corresponding amount in a reference sample, and correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status of the patient, which anticipates the genus of a method of determining disease status of a patient suffering from a disease characterized by aberrant expression of one or more ErbB cell surface receptor complexes comprising measuring directly in a patient sample an amount of each of one or more ErbB cell surface receptor complexes in the pending claims. "A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus." The species in that case will anticipate the genus. In re Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. **Conclusion:** No claims are allowed. Claims 1-7, 14, 15, 30-34, 37, 38, and 40-43 are rejected under 35 U.S.C. 112, first paragraph, and appear to be free of the prior art. The closest prior art appears to be Alimandi et al (Oncogene, 1995, 10:1813-1821). Alimandi et al teach Her2 and Her 3 cooperate in neoplastic transformation, that cooperation between the two involves heterodimerization, and that Her3 activates Her2 transforming potential at intermediate expression levels and substantially enhances neoplastic transformation (abstract; p. 1819, col. 1). Alimandi et al do not teach or suggest detection of ErbB cell surface receptor complexes in patient samples to determine disease status.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER